Current Therapies in the Management of Parkinson's Disease Psychosis

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Disclosure

- Dr. Brent Curry has no relevant conflicts of interest to disclose

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Learning Objectives

After the completion of this presentation, the participant should be able to:

1. Understand the pathophysiology behind Parkinson's Disease Psychosis
2. Identify treatment options for the management of Parkinson's Disease Psychosis
3. Summarize the research on the newest available agent for the treatment of Parkinson's Disease Psychosis

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Abbreviations

AIMS	Abnormal Involuntary Movement Scale
BPRS	Brief Psychiatric Rating Scale
CGI-S	Clinical Global Impression Scale
COMT	Catechol-O-methyl transferase
MAO-B	Monoamine oxidase B
MMSE	Mini-Mental Status Exam
NIMH	National Institute of Mental Health
NINDS	National Institute of Neurological Disorders and Stroke
NPI	Neuropsychiatric Inventory
PANSS	Positive and Negative Syndrome Scale
PDP	Parkinson's Disease Psychosis
SAPS	Scale for the Assessment of Positive Symptoms
UPDRS	Unified Parkinson's Disease Rating Scale

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Parkinson's Disease Psychosis

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What is PDP?

- Part of spectrum of neuropsychiatric disorders in Parkinson's disease patients
- NINDS/NIMH Criteria for PDP:
  - Primary diagnosis of Parkinson's disease
  - Symptoms occur after onset of Parkinson's
  - Presence of at least one psychotic symptom
  - Recurrent or continuous for one month
- Associated with:
  - Patient morbidity
  - Caregiver burden
  - Early mortality

Starkstein SE, Brockman S, Haylow BD. Psychiatric syndromes in Parkinson's disease. Curr Opin Psychiatry 2012; 25:468-472.
Chang Anna, Fox SH. Psychosis in Parkinson's Disease. Drugs 2016; 76:193-1118
Ravina B, Marder K, Fernandez HH, et al. Diagnostic criteria for psychosis in Parkinson's disease. Mov Disord. 2007;22(8):1061-8.

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Prevalence of PDP

- Prevalence varies widely → from 16 % up to 75%
  - Recent study reported prevalence as 60% in 116 Parkinson's disease patients in outpatient clinic setting
  - Similar study in 250 community-based Parkinson's disease patients reported prevalence as 26%
- In all studies, visual hallucinations are the most common psychotic symptom
- Auditory hallucinations are less common and delusions even less common

Chang Anna, Fox SH. Psychosis in Parkinson's Disease. Drugs 2016; 76:193-1118

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Psychotic Symptoms

- Consist of:
  - Illusions
  - False sense of presence
  - Hallucinations (visual and auditory)
  - Delusions
- Insight usually retained initially
- The phenomenology of psychotic symptoms unique to Parkinson's disease → suggest disease-specific vs. drug-induced etiology

Chang Anna, Fox SH. Psychosis in Parkinson's Disease. Drugs 2016; 76:193-1118

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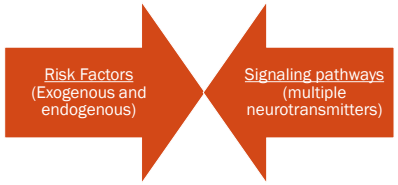
Pathophysiology

- Dopaminergic system considered to play pivotal role in pathophysiology
- Link with medications is inconsistent
- Complex interplay



Zahodne LB, Fernandez HH. Pathophysiology and treatment of psychosis in Parkinson's disease. Drugs Aging. 2008; 25(8):665-82.
Chang Anna, Fox SH. Psychosis in Parkinson's Disease. Drugs 2016; 76:193-1118

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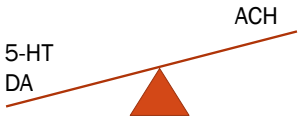
Pathophysiology

- Neuropathology
- Neuroimaging
- Neurotransmitters
- Neuro-signaling pathways



Chang Anna, Fox SH. Psychosis in Parkinson's Disease. Drugs 2016; 76:193-1118

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Treatment Options for Parkinson's Disease Psychosis

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Treatment Considerations

- Rule out other causes of psychosis
- Relationship between symptoms and medications difficult to interpret and separate
- Limit use of dopaminergic medications → symptoms may persist after medications stopped or reduced
- Ensure that motor function is maintained
  - Continue carbidopa/ levodopa and readjust

Levin J, Hasan A, Höglinger GU. Psychosis in Parkinson's disease. *J Neural Transm (Vienna)*. 2016;123(1):45-50.

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Review of Medications

- Limit use of non-essential non-Parkinson's disease medications:
  - Tricyclic antidepressants
  - Bladder antispasmodics
  - Benzodiazepines
  - Muscle relaxants
  - Opioids
- Consider tapering and eliminating:
  - Anticholinergics
  - MAO-B inhibitors
  - Amantadine
  - Dopamine Agonists
  - COMT inhibitors

Chang Anna, Fox SH. Psychosis in Parkinson's Disease. Drugs 2016; 76:193-1118

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Guideline Recommendations

AMERICAN ACADEMY OF NEUROLOGY®

- Clozapine should be considered for patients with Parkinson's disease and psychosis (Level B)
  - Associated with agranulocytosis and absolute neutrophil count must be monitored
- Olanzapine should not be routinely considered for patients with Parkinson's disease and psychosis (Level B)
- Quetiapine may be considered for patients with Parkinson's disease and psychosis (Level C)

Miyasaki JM, Shannon K, Voon V, et al. Practice Parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson disease. Neurology. 2006;66(7):996-1002.

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Other Recommendations

The *Movement* Disorder Society

	Efficacy	Safety	Practice Implications
Clozapine	Efficacious	Acceptable risk w/ specialized monitoring	Clinically useful
Olanzapine	Unlikely efficacious	Unacceptable risk	Not useful
Quetiapine	Insufficient evidence	Acceptable risk w/o specialized monitoring	Investigational

Seppi K, Weintraub D, Coelho M, et al. The Movement Disorder Society Evidence-Based Medicine Review Update. Mov Disord. 2011; 26 Suppl 3:S42-80.

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Unified Parkinson's Disease Rating Scale (UPDRS)

Part I	Evaluation of mentation, behavior, and mood
Part II	Self-evaluation of the activities of daily life (ADLs) including speech, swallowing, handwriting, dressing, hygiene, falling, salivating, turning in bed, walking, and cutting food
Part III	Clinician-scored monitored motor evaluation
Part IV	Complications of therapy
Part V	Hoehn and Yahr staging of severity of Parkinson's disease
Part VI	Schwab and England ADL scale

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Ratings Scales

Scale		Measure	Rating
Brief Psychiatric Rating Scale	BPRS	Measures psychiatric symptoms	18-24 symptoms rated from 1-7
Neuropsychiatric Inventory	NPI	Assesses neuropsychiatric symptoms of those with Alzheimer's	Behaviors scored based on frequency, severity and of causing caregiver distress
Positive and Negative Syndrome Scale	PANSS	Measures symptom severity of schizophrenia	30 different symptoms rated from 1-7
Scale for Assessment of Positive Symptoms	SAPS	Measures positive symptoms in schizophrenia	Separate symptoms within 4 domains rated from 0-5

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Clozapine
Pollak et al. (2004)

Design

- 4-week, randomized, double-blind, parallel-group comparison of clozapine and placebo
- Followed by 12-week clozapine open phase and then 1-month washout period in 60 patients
- Clozapine titrated from 6.25 mg/day and increased a maximum of three 12.5 mg steps each week up to a maximum of 50 mg/day

Outcomes

- Primary efficacy outcome was CGI-S
- The positive subscore of PANSS used as secondary efficacy parameter
- UPDRS and MMSE as safety outcomes

Pollak P, Tison F, Rascol O, et al. Clozapine in drug induced psychosis in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2004; 75:689–695.

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Clozapine
Pollak et al. (2004)

Results

- Mean dose of clozapine was ~36 mg/day at end of double blind period
- Mean scores on CGI-S improved by 1.8 for clozapine group compared with 0.6 for placebo group (*P* = 0.001)
- Mean positive subscore of PANSS improved by 5.6 for clozapine group and 0.8 for placebo group (*P* < 0.0001)

Limits

- 19/25 (76%) experienced a relapse within one month of washout period
- The UPDRS motor and MMSE mean scores did not change significantly in either group

Pollak P, Tison F, Rascol O, et al. Clozapine in drug induced psychosis in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2004; 75:689–695.

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Clozapine vs. Quetiapine
Morgante et al. (2004)

Design

- 12-week randomized, rater-blinded trial
- 40 patients with PDP treated with either clozapine (n=20) or quetiapine (n=20)
- Clozapine started at 6.25 mg/day and titrated up to 50 mg/day
- Quetiapine started at 25 mg/day and titrated up to 200 mg/day

Outcomes

- Severity of psychosis assessed using:
  - BPRS total, BPRS 5-Items, and CGI-S
- Motor impairment assessed using UPDRS-III and dyskinesias assessed using AIMS

Morgante L, Epifanio A, Spina E, et al. Quetiapine and clozapine in parkinsonian patients with dopaminergic psychosis. Clin Neuropharmacol. 2004;27:153–156.

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Demographic and Clinical Features of the Patients Completing the Study

Features		Quetiapine (n=20)	Clozapine (n=20)	Differences Between Treatment Groups
BPRS total	Baseline	37.1 ± 6.1	37.4 ± 5.4	NS
	Endpoint	38.7 ± 4.2	26.7 ± 3.6	NS
BPRS (5 items)	Baseline	15.5 ± 3.4	16.4 ± 2.6	NS
	Endpoint	8.4 ± 1.5	8.5 ± 2.0	NS
CGI-S	Baseline	3.6 ± 0.7	3.8 ± 0.8	NS
	Endpoint	2.1 ± 0.6	1.9 ± 0.6	NS
UPDRS-III	Baseline	53 ± 11	58 ± 9.4	NS
	Endpoint	54 ± 11	56.7 ± 9.2	NS
AIMS	Baseline	7.8 ± 2	7.2 ± 2.1	NS
	Endpoint	6 ± 1.3	5.4 ± 1.3	NS

Morgante L, Epifanio A, Spina E, et al. Quetiapine and clozapine in parkinsonian patients with dopaminergic psychosis. Clin Neuropharmacol. 2004;27:153–156.

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Clozapine vs. Quetiapine
Morgante et al. (2004)

Results

- Mean dosages of 91 mg/day in quetiapine arm and 26 mg/day in clozapine arm
- Psychosis scores improved significantly in both groups as recorded on both BPRS and CGI-S ($P < .001$)
- UPDRS-III scores remained stable in both groups
- Statistically significant decrease in dyskinesia ($P < 0.05$) in both groups

Limits

- Motor worsening was reported in 3 patients on quetiapine
- 5/40 (12.5%) patients dropped out due to adverse effects
  - 3 patients in clozapine arm, 2 patients in quetiapine arm

Morgante L, Epifanio A, Spina E, et al. Quetiapine and clozapine in parkinsonian patients with dopaminergic psychosis. Clin Neuropharmacol. 2004;27:153–156.

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Clozapine vs. Quetiapine
Merims et al. (2006)

Design

- 22-week parallel-group, randomized controlled trial comparing quetiapine (n = 13) and clozapine (n = 14)
- Dose adjustments gradually increased every 2 weeks during the first 10 weeks (maximal 50 mg/day for clozapine and 150 mg/day for quetiapine) until psychosis considered under "satisfactory control"

Outcomes

- Primary endpoints were selected items (hallucinations and delusions) from NPI and CGI-C questionnaires
- Assessments done by a blinded neuropsychologist
- Motor worsening assessed using UDPRS

Merims D, Balas M, Peretz C, Shabtai H, Giladi N. Rater-blinded, prospective comparison: quetiapine versus clozapine for Parkinson's disease psychosis. Clin Neuropharmacol. 2006;29:331–337.

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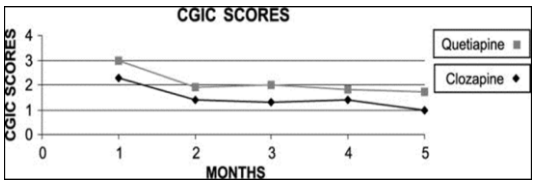
The CGIC (mean scores) from baseline scores over time in the 2 treatment groups



Merims D, Balas M, Peretz C, Shabtai H, Giladi N. Rater-blinded, prospective comparison: quetiapine versus clozapine for Parkinson's disease psychosis. Clin Neuropharmacol. 2006;29:331–337.

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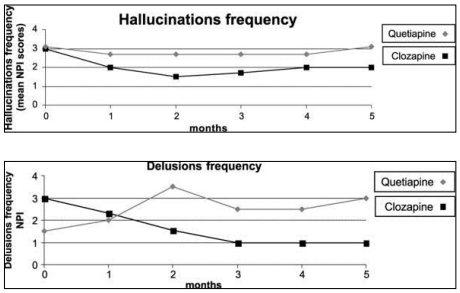
Hallucinations and delusions frequency (mean NPI scores) over time in both treatment groups



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Clozapine vs. Quetiapine
Merims et al. (2006)

Results

- 11 patients (~80%) from each arm reached "satisfactory control"
- Mean dose was 91 mg/day for quetiapine and 13 mg/day for clozapine
- No worsening in motor symptoms as measured by UPDRS in either treatment arm

Limits

- Only 7/14 patients randomized to receive clozapine and 9/13 randomized to receive quetiapine completed the study
  - One patient developed severe neutropenia with clozapine and 2 others discounted due to decreases in leukocytes

Merims D, Balas M, Peretz C, Shabtai H, Giladi N. Rater-blinded, prospective comparison: quetiapine versus clozapine for Parkinson's disease psychosis. Clin Neuropharmacol. 2006;29:331–337.

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Quetiapine

Study	Design	Intervention	Results	Limits
Ondo et al. (2005)	Double-blind, placebo-controlled, parallel-group study	Patients randomized in a 2:1 ratio to 12 weeks of treatment with quetiapine (n = 21, up to 200 mg/day) or placebo (n = 10)	None of the hallucinations, psychosis, or motor impairment assessments changed significantly on quetiapine	4/17 (24%) patients on quetiapine that completed study reported subjective worsening
Rabey et al. (2007)	Double-blind, placebo-controlled, parallel-group	12-week trial investigating total of 58 patients (quetiapine n = 30, mean dosage 119.2 ± 56.4 mg/day; placebo n = 28)	Compared to placebo none of BPRS or CGI-S scores changed significantly on quetiapine	High dropout rate of 45% (n = 26) primarily due to lack of efficacy

Ondo W, Tintner R, Voung K, Lai D, Ringholz G. Double-blind, placebo-controlled, unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease. Mov Disord. 2005; 20:958–963.
Rabey J, Prokhorov T, Miniovitz A, Dobronevsky E, Klein C. Effect of quetiapine in psychotic Parkinson's disease patients. Mov Disord. 2007; 22:313–318.

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Olanzapine

Study	Design	Intervention	Results	Limits
Breier et al. (2002)	2 placebo-controlled, double-blind, parallel-group randomized controlled trials	Patients randomized 1:1 in the U.S. study (n= 83), and 2:1 in the European study (n= 77) to receive olanzapine (mean dosage 4.2 mg ± 2.6 and 4.1 mg ± 2.0, respectively) or placebo	No significant treatment group differences in any psychosis ratings on BPRS were found in either study	Motor function worsened significantly in patients on olanzapine compared to placebo as measured by UPDRS
Ondo et al. (2002)	Double-blind, placebo-controlled, parallel-group, randomized controlled trial	30 patients with PDP underwent 9 weeks of treatment with olanzapine (mean dosage 4.6 mg/day) or placebo (2:1 ratio)	Failed to detect significant differences between olanzapine and placebo in any of psychosis measures	Significant worsening of UPDRS motor scores in the olanzapine arm

Breier A, Sutton V, Feldman P, et al. Olanzapine in the treatment of dopaminmetic-induced psychosis in patients with Parkinson's disease. Biol Psychiatry. 2002; 52:438–445.
Ondo W, Levy J, Vuong K, Hunter C, Jankovic J. Olanzapine treatment for dopaminergic-induced hallucinations. Mov Disord. 2002; 17:1031–1035.

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Other Atypical Antipsychotics

- Open-label trial involving 14 patients with PDP treated with **aripiprazole**
  - 6/14 (43%) patients experienced improvement in psychosis
  - 8/14 (57%) patients discontinued treatment due adverse effects
- 4-week, randomized, single-blind, open-label, parallel comparison of **ziprasidone and clozapine** in 16 patients with PDP
  - 14/16 patients completed the study → 8 patients on clozapine and 6 patients on ziprasidone
  - Ziprasidone seemed to be at least as effective as clozapine as psychotic symptoms reduced in both groups

Friedman JH, Berman RM, Goetz CG, et al. Open-label flexible-dose pilot study to evaluate the safety and tolerability of aripiprazole in patients with psychosis associated with Parkinson's disease. Movement Disorders. 2006; 21 (12):2078–81.
Pintor L, Valldeoriola F, Baillès E et al. Ziprasidone versus clozapine in the treatment of psychotic symptoms in Parkinson Disease. Clin Neuropharm 2012;35: 61-66

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NUPLAZID™
(pimavanserin) tablets

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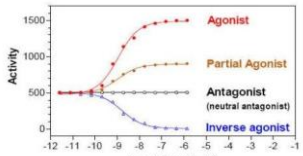
Mechanism of Action

- Acts as an inverse agonist and antagonist
- High affinity for 5-HT_{2A} receptors and low affinity for 5-HT_{2C} receptors
- No affinity for 5-HT_{2B}, dopaminergic (including D_2), muscarinic, histaminergic, or adrenergic receptors



Nuplazid (pimavanserin) [prescribing information]. San Diego, CA: Acadia Pharmaceuticals Inc; April 2016.

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Pharmacokinetics

- Distribution: V_d: 2,173 L
- Protein binding: ~95%
- Metabolism: Primarily via CYP3A4 and CYP3A5; forms active N-desmethylated metabolite
- Elimination half-life:
  - Pimavanserin: ~57 hours
  - N-desmethylated metabolite: ~200 hours
- Time to peak: 6 hours (median: 4 to 24 hours)
- Excretion: Feces (<2%); urine (<1% as unchanged)

Nuplazid (pimavanserin) [prescribing information]. San Diego, CA: Acadia Pharmaceuticals Inc; April 2016.

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NUPLAZID™ (pimavanserin) tablets

- **Dose:** 34 mg/day taken with or without food
  - Dose adjustment needed with concomitant therapy of strong CYP3A4 inhibitors/ inducers
  - Not recommended in severe renal/ hepatic impairment
- **AEs:** CNS depression, orthostatic hypotension, QTc-prolongation, peripheral edema, confusion, hallucinations, abnormal gait, nausea, constipation

Nuplazid (pimavanserin) [prescribing information]. San Diego, CA: Acadia Pharmaceuticals Inc; April 2016.

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Studies Evaluating Pimavanserin

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Meltzer et al. (2010) – Phase II study

Design

- Double-blind, randomized multi-center 28-day study
- Tolerability and efficacy of pimavanserin (doses up to 60 mg/day) compared to placebo in 60 patients with PDP

Outcomes

- Antipsychotic efficacy evaluated using SAPS
- SAPS total domain score was chosen as principal outcome measure for efficacy
- Motor function evaluated using UPDRS

Meltzer HY, Mills R, Revell S, et al. Pimavanserin, a serotonin(2A) receptor inverse agonist, for the treatment of parkinson's disease psychosis. Neuropsychopharmacology. 2010;35(4):881-92.

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Meltzer et al. (2010):

Mean (SD) Baseline and Day 28 SAPS Scores

Change from Baseline (Screening Visit) to Day 28

Parameter	Pimavanserin (n=24)		Placebo (n=28)		LS mean difference	95% CI	*P*-value	Effect size
	Base	Day 28	Base	Day 28				
SAPS total (H+D) domain score	16.7 (7.45)	11.0 (11.09)	17.9 (11.79)	16.8 (14.35)	−4.6	−10.0, 0.7	0.09	0.56

Meltzer HY, Mills R, Revell S, et al. Pimavanserin, a serotonin(2A) receptor inverse agonist, for the treatment of parkinson's disease psychosis. Neuropsychopharmacology. 2010;35(4):881-92.

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Meltzer et al. (2010) – Phase II study

Results

- Pimavanserin did not differentiate from placebo with regard to motor impairment, sedation, hypotension, or other side effects

Limits

- Principal measures of efficacy of antipsychotic response, the SAPS total domain score, only showed a trend

Meltzer HY, Mills R, Revell S, et al. Pimavanserin, a serotonin(2A) receptor inverse agonist, for the treatment of parkinson's disease psychosis. Neuropsychopharmacology. 2010;35(4):881-92.

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Cummings et al. (2014) – Phase III study

Design

- 6 week, randomized, double-blind, placebo-controlled
- After 2 week non-pharmacological lead-in phase, patients randomly allocated (1:1) to receive pimavanserin 40 mg/day (n= 90) or placebo (n=95)

Outcomes

- Antipsychotic benefit evaluated using SAPS-PD
- Safety and tolerability in all patients

Cummings J, Isaacson S, Mills R, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomized, placebo-controlled phase 3 trial. Lancet 2014;383:533-40.

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Cummings et al. (2014) – Phase III study

Results

- Pimavanserin was associated with a -5.79 decrease in SAPS-PD scores compared with -2.73 for placebo (difference -3.06, 95% CI -4.91 to -1.20; *P* =0.001)
- Pimavanserin was well tolerated with no significant safety concerns or worsening of motor function

Limits

- 10 patients in the pimavanserin group discontinued because of an adverse event
  - 4 patients experiencing hallucinations within 10 days of start of pimavanserin

Cummings J, Isaacson S, Mills R, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomized, placebo-controlled phase 3 trial. Lancet 2014;383:533-40.

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Yasue et al. (2015)

Design

- Meta-analysis of randomized placebo-controlled trials
- Included 417 drug-treated and 263 placebo-treated PDP patients over 4 trials (2 unpublished trials)

Outcomes

- Comparison of SAPS-H+D scores (primary)
- Comparison of SAPS-H, SAPS-D, UPDRS-II+III scores, discontinuation rates, and individual adverse events (secondary)

Yasue I, Matsunaga S, Kishi T, Fujita K, Iwata N. Serotonin 2A Receptor Inverse Agonist as a Treatment for Parkinson's Disease Psychosis: A Systematic Review and Meta-analysis of Serotonin 2A Receptor Negative Modulators. J Alzheimers Dis. 2015;50(3):733-40

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Yasue et al. (2015)

Results

- Pimavanserin significantly decreased SAPS-H+D scores compared to placebo (difference -2.26, 95% CI -3.86 to -0.67; $P=0.005$)
- Pimavanserin was superior to placebo for reducing SAPS-H and SAPS-D scores

Adverse Events

- Pimavanserin was associated with less orthostatic hypotension than placebo
- There were no significant differences in rates of all-cause discontinuation, adverse events, death, UPDRS scores, and incidences of individual adverse events

Yasue I, Matsunaga S, Kishi T, Fujita K, Iwata N. Serotonin 2A Receptor Inverse Agonist as a Treatment for Parkinson's Disease Psychosis: A Systematic Review and Meta-analysis of Serotonin 2A Receptor Negative Modulators. J Alzheimers Dis. 2015;50(3):733-40

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A Review of the Treatment Options

Antipsychotic Medication	Decrease in Psychotic Symptoms	Lack of Motor Adverse Effects
Clozapine	+	+
Quetiapine	+ / –	+ / –
Olanzapine	—	—
Pimavanserin	+ / –	+

+ = Positive outcomes in trials +/– = Mixed outcomes in trials – = Negative outcomes in trials

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Treatment Considerations with Pimavanserin

- Cost → 17 mg (60): AWP = $2,340
- Currently only available through restricted access program and limited wholesalers
- Significant drug-drug interactions with CYP 3A4 inducers and inhibitors
- Avoid use in those with QT prolongation or on other drugs that can prolong QT interval
- Concerns about safety including the rates for severe adverse effects and deaths
- Post hoc analysis of open-label extension study showed significant increase in mortality of those taking concurrent antipsychotics (IRR 4.20, 95% CI 2.13-7.96)

Ballard C, Isaacson S, Mills R, et al. Impact of Current Antipsychotic Medications on Comparative Mortality in People With Parkinson Disease Psychosis. J Am Med Dir Assoc. 2015;16(10):898.e1-7.

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Place in Therapy for Pimavanserin

- No other FDA-approved drugs for PDP
- Other treatment options have several limitations and concerns for safety and adverse effects
- Unique mechanism of action opens door for further research
- Potential to be first choice treatment option for PDP

Hermanowicz S, Hermanowicz N. The safety, tolerability and efficacy of pimavanserin tartrate in the treatment of psychosis in Parkinson's disease. Expert Rev Neurother. 2016; 16(6):625-33

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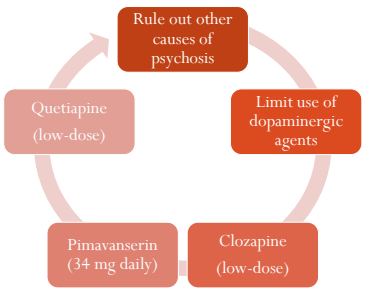
Management of PDP



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Patient Case

In the geriatric clinic where you are the clinical pharmacist, a provider approaches you asking for a recommendation for one of his patients after a recent visit. The patient is a 70-year-old man with a 10-year history of Parkinson's disease being treated with carbidopa/levodopa (25/250-mg tablets PO Q4H) and pramipexole (1.5 mg PO Q8H). He had not been experiencing motor fluctuations. But during the visit, the patient remarked that "the leprechauns had been coming out more than usual in the few last weeks." The patient's family explained that he had been seeing small people dressed in costumes sitting in his living room over the last few months. The patient thought "the leprechauns" were amusing and did not report being bother by these hallucinations.

Adopted from: Salter BC, Anderson KE, Weiner WJ. Psychosis in Parkinson's disease: case studies. Neurol Clin. 2006;24(2):363-9

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  - Stephen Saklad, Pharm.D., BCPP

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